as originally filed. Support may be found throughout the specification and in the originally filed claims. Specifically, support for the transgenic mice and methods of producing the transgenic mice recited in claims 21-22 and 24-25 can be found, for example, at page 8, line 24 through page 15, line 12, and at page 51, lines 1-23, of the specification. Support for the cell or tissue recited in claim 23 may further be found, for example, at page 11, line 1 through page 14, line 14 of the specification. Support for the targeting construct recited in claim 26 may be found, for example, at page 8, line 24 through page 10, line 30 of the specification. Finally, support for the murine embryonic stem cell recited in claim 27 may be found, for example, at page 11, line 1 through page 14, line 14.

The amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

Upon entry of the amendment, claims 21-27 are pending in the instant application.

II. Claim Objections

Claim 2 was objected to under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 2 has been cancelled. In view of the cancellation of claim 2, the Examiner's objection is no longer relevant, and the Applicant therefore requests withdrawal of the objection. The Applicant submits that new claims 21-27 and are in proper form as required under 37 C.F.R. 1.75(c).

II. Rejections

A. Rejections under 35 U.S.C. § 112, first paragraph

1. Enablement

Claims 1-10 and 17-19 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims. The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 1-10 and 17-19, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Specifically, in the rejection, the Examiner asserts that due to the nature of the invention and the breadth of the claims, the specification does not provide an enabling disclosure for the full scope of transgenic animals and/or knockout mice comprising any disruption in any DEZ receptor gene as claimed. Further, according to the Examiner, the specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine DEZ receptor gene of SEQ ID NO:1, wherein the disruption results in loss of function of the DEZ receptor gene. In addition, the Examiner asserts that, due to the unpredictability of the phenotype of a transgenic animal, the specification is not enabling for transgenic animals, including mice, which exhibit no phenotype or a phenotype other than that disclosed in the application. Finally, according to the Examiner, the specification fails to provide an enabling disclosure for the preparation of transgenic animals of a species other than mice due to the limited knowledge of ES cell technology in other species.

The Applicant respectfully disagrees with the Examiner's conclusions. However, claims 1-10 and 17-19 have been cancelled. The Applicant submits that the specification provides sufficient enabling disclosure for the transgenic mice and methods of producing the transgenic mice as currently recited in new claims 21-27. More particularly, the scope of the current claims, which encompass transgenic mice comprising a homozygous disruption in the endogenous murine DEZ receptor gene, which disruption leads to a lack of production of functional DEZ receptor and a phenotype of decreased agility or coordination, is sufficiently enabled by the instant specification.

As this rejection under 35 U.S.C. § 112, first paragraph, of claims 1-10 and 17-19 is no longer relevant as a result of the cancellation of these claims, and new claims 21-27 are fully enabled by the teachings of the specification as noted above, Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

2. Written Description

Claims 1-10 and 17-19 were further rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey that the inventor had possession of the invention at the time of filing of the instant application. The Applicant respectfully traverses this rejection under 35 U.S.C. § 112,

first paragraph, in light of the cancellation of claims 1-10 and 17-19 and the arguments presented below.

Specifically, the Examiner asserts that the specification does not provide or point to a written description of a genus of DEZ receptor genes recited in the claims. The Applicant disagrees with the Examiner's assertion that a genus of DEZ receptor genes is recited in the claims. The claims, and in particular, new claims 21-27, recite an endogenous murine DEZ receptor gene, which is sufficiently described and/or defined in the specification as originally filed. For example, the Applicant refers the Examiner to a description of the DEZ receptor gene located at page 6, lines 21-24 of the specification.

As claims 1-10 and 17-19 have been cancelled, and the originally filed specification adequately demonstrates possession of the invention recited in new claims 21-27 as required by 35 U.S.C. § 112, the written description rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant. The Applicant respectfully requests withdrawal of this rejection.

B. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 9 and 10 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The Applicant respectfully traverses each rejection under 35 U.S.C. § 112, second paragraph. However, in light of the cancellation of claims 1-4, 9 and 10, the rejection is no longer relevant.

In particular, claims 1-4 and 10 were rejected because the Examiner asserted that the arrangement of the targeting construct was allegedly unclear. Although the Applicant disagrees that the arrangement is unclear, the Applicant submits that new claim 26 clearly defines the arrangement and elements of the targeting construct.

Claims 1-4 were further rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the terms "selectable marker," "selection marker" or "screening marker" render the claims indefinite because it is unclear how a marker protein can be inserted into a targeting construct. The Examiner suggests using the term "selectable marker gene." Although the Applicant respectfully disagrees in that a person skilled in the relevant art would be able to ascertain the intended meaning of each of the foregoing terms, the Applicant adopts the Examiner's suggestion in new claim 26 in an effort to advance prosecution.

Claim 2 was rejected under 35 U.S.C. § 112, second paragraph, because it is allegedly unclear how the term "screening marker" differs from "selection marker" as recited in its parent claim 1. The Applicant respectfully traverses this rejection in that the specification clearly defines and distinguishes each term as well as provides examples of each (see, for example, page 7, lines 10-15 and pages 12-14 of the specification). Moreover, new claim 26 does not recite a screening marker, rendering the Examiner's rejection moot.

Claim 9 was rejected on the basis that the word "derived" renders the claim indefinite. The Applicant respectfully disagrees in that the meaning of the term "derived" in relation to cells derived from a transgenic mouse is clear and definite to one skilled in the art. In addition, the term has been clearly described in the specification at, for example, page 2, lines 26-29. However, new claim 23 does not use the term "derived" and therefore this rejection is no longer relevant.

The Applicant has traversed the rejections under 35 U.S.C. § 112, second paragraph. Claims 1-4, 9 and 10 have been cancelled, and new claims 21-27 are definite and clearly point out and distinctly claim the subject matter regarded as the invention, for at least the reasons provided above. As the rejection under 35 U.S.C. § 112, second paragraph, is no longer relevant, withdrawal of the rejection is respectfully requested.

C. Rejections under 35 U.S.C. § 103

Claims 1-10 and 19 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Mansour *et al.*,1998, *Nature,* 336(24):348-352 ("Mansour") in view of Methner *et al.,* 1997, *Biochem and Biophys Res Commun.,* 233(2):336-342 ("Methner") and Murphy *et al.,* 1998, *Current Opinion in Drug Discovery and Development,* 1(2):192-199 ("Murphy"). Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 1-10 and 19, the rejection under 35 U.S.C. § 103 is no longer relevant.

Applicant submits that new claims 21-27 are non-obvious over the teachings of the prior art references. More particularly, the claimed invention relates to the *in vivo* mammalian characterization of the function of the DEZ receptor gene, and provides transgenic mice and cells comprising a disruption in the endogenous murine DEZ receptor gene and methods and compositions relating thereto, all of which are not obvious in view of the sole or combined teachings and disclosures of the references cited by the Examiner.

According to the Examiner, Mansour teaches a strategy for targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells, and subsequent generation of knockout mice. The disclosure of Mansour relates to a general method for isolating embryonic stem cells containing a targeted mutation in an endogenous gene. More particularly, Mansour teaches the targeted disruption of the *hprt* gene and the proto-oncogene *int-2* in mouse embryonic stem cells by homologous recombination using targeting constructs specific for these genes. The Examiner states in the rejection that the teachings of Mansour provide a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available.

Methner, as characterized by the Examiner, teaches the cloning and characterization of a novel G-protein coupled receptor, the DEZ receptor, from a cell line and a cDNA library of adult mouse brain, and provides the nucleic acid sequence encoding the DEZ receptor gene.

The Examiner asserts that Murphy teaches that GPCRs are the major structures through which physiological signals involving cellular and organism homeostasis are transduced across the cell membrane, and represent the largest single group of drug targets. The Examiner further asserts that Murphy teaches that the physiological and pathophysiological function of GPCRs must be studied before the successful development of therapeutic compounds targeting these receptors.

In order to establish a *prima facie* case of obviousness, the Examiner must three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) must teach or suggest all the claim limitations. See MPEP §2143.

The Examiner asserts that the ordinary artisan would have been motivated to combine the teachings of the prior art references to study the physiological and pathophysiological function of the DEZ receptor in order to make it a therapeutic target for developing new drugs as is allegedly taught by Murphy *et al.*. The Applicant respectfully disagrees. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See MPEP 2143.01. The Applicant submits that Murphy does not suggest the desirability of disrupting the DEZ receptor in a mouse. In fact, Murphy teaches away from the presently claimed invention or at the very least suggests that combination of the reference teachings would be undesirable or disadvantageous. Murphy

suggests that gene knockout studies represent a double-edged sword, in that there exists the possibility that the knockout will result in no phenotype, or a lethal phenotype, both of which are not readily interpretable in the context of disease models (see page 192, column 2, paragraph 2). Murphy teaches that systems that utilize GPCR-specific agonists are advantageous. In addition, Murphy suggests that the preferred method for studying the function of orphan GPCRs is functional expression in the yeast system (*Saccharomyces cerevisiae* - extensively described starting on page 194), and states that such heterologous expression systems "offer unique advantages over other approaches that employ mammalian cells (see page 196, Conclusion). Accordingly, one skilled in the art reading the Murphy reference would be disinclined or discouraged from using knockout mice to determine the function of orphan GPCRs such as the DEZ receptor. Therefore, the Examiner has failed to provide sufficient evidence in Murphy of the motivation or suggestion to combine the prior art references required to establish a case of *prima facie* obviousness.

The Examiner further asserts that one of ordinary skill in the art would have a reasonable expectation of success to make a DEZ receptor knockout mouse because of the teaching of Mansour, who teaches a general method of generating a homozygous mutation of any gene in a mouse, and Methner, who provides the sequence information for the DEZ receptor. The Applicant respectfully disagrees. Mansour does not teach, suggest or contain any disclosure regarding orphan GPCRs, let alone the DEZ receptor. That Methner simply provides the sequence of murine DEZ receptor does not cure that failing. In any case, the Applicant has cancelled claims 1-10 and 19, and submits that one of ordinary skill in the art would not have a reasonable expectation of success in combining the cited references to create the invention as recited in new claims 21-27.

Finally, in order to establish a *prima facie* case of obviousness, the Examiner must also show that the prior art references teach or suggest all of the claimed limitations. As described above, the disclosure of Mansour is limited to providing a general approach for isolating embryonic stem cells and provides a model for the production of homozygous mutation in a gene. Methner teaches the cloning and characterization of the DEZ receptor and provides the nucleic acid sequence of the DEZ receptor. The teachings of Murphy merely discuss the status of GPCRs as a group as important structures in cell membrane signal transduction and the need for their characterization in order to develop them as therapeutic drug targets.

However, neither Mansour, Methner nor Murphy, alone or in combination, teaches all of the limitations as presently claimed. As acknowledged by the Examiner, Mansour provides no disclosure or teaching of how to make a DEZ receptor gene targeting construct or a DEZ receptor gene knockout mouse. (See Office Action, page 12). More particularly, Mansour does not teach or suggest a targeting construct containing a DNA sequence homologous to a DEZ receptor gene as recited in the pending claims. Nor, does Mansour teach a transgenic mouse comprising a disruption in a DEZ receptor gene, a method of producing the transgenic mouse, or cells or tissues as claimed by the present invention. Likewise, Methner does not provide any teaching or suggestion relating to targeted disruptions in the DEZ receptor gene. More particularly, the disclosure of Methner fails to provide any teaching or suggestion that relates to transgenic mice, cells, tissues, or targeting constructs, and in particular to those recited in the pending claims. Further, Murphy fails to provide any teaching or suggestion of the DEZ receptor gene, disruption of this gene, or any methods or compositions related thereto as is currently claimed by the instant invention.

Taken together, the disclosures of Mansour, Methner and Murphy are devoid of any teaching or suggestion of disrupting the DEZ receptor gene, and in particular, are deficient of any teachings or suggestions of the transgenic mice, targeting constructs, tissues, cells, and methods as recited in the pending claims. More particularly, the disclosures of Mansour, Methner and Murphy, alone or combined, do not teach or suggest in any way transgenic mice comprising a disrupted DEZ receptor gene, wherein such transgenic mice lack production of functional DEZ receptor and exhibit a phenotype, and in particular a phenotype of decreased agility or coordination, methods of producing such transgenic mice, or tissues and cells comprising the disrupted DEZ receptor gene as is claimed by the present invention.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 1-10 and 19, and new claims 21-27 are not obvious in view of the teachings of Mansour, Methner and Murphy, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-173.

Respectfully submitted,

Date: 2/5/03

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